UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,212	01/12/2007	Kenzo Muramoto	082368-008200US	3556

20350 7590 03/17/2010

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
03/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,212	MURAMOTO ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *2,4-6,8,10,11 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,9,12-15 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

This Office Action is in response to Applicant's Restriction Requirement remarks filed on November 30, 2009. Claim(s) 1-25 are pending. Claim(s) 2, 4-6, 8, 10, 11, and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant's election of Group II drawn to a method for treating or preventing multiple sclerosis, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound represented by formula (I), or a pharmaceutically acceptable salt or hydrate thereof, wherein the bond between Z^1 and Z^2 is double and election of species of component of formula I (2-(3-aminopiperidin-l-yl)-3-(2- butynyl)-5-methyl-3,5-dihydroimidazo[4,5-d]pyridazin-4-one, compound 3X on page 109 of the specification) without traverse of the restriction requirement in the reply is acknowledged. The requirement is deemed proper and is therefore made FINAL. Claim(s) 1, 3, 7, 9, 12-15, and 17-25 are examined herein insofar as they read on the elected invention and species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 7, 9, 12-15, and 17-25 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of multiple sclerosis, does not reasonably provide enablement for the prevention of multiple sclerosis as recited in these claims.

The instant claims are drawn to a pharmaceutical composition and a method for the prevention of multiple sclerosis. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant invention pertains to a method for the prevention of multiple sclerosis.

The state of the prior art:

The skilled artisan would view that the prevention of one or more symptoms of multiple sclerosis totally, absolutely, or permanently, is highly unlikely, since one cannot guarantee that the multiple sclerosis will always be prevented.

The relative skill of those in the art:

The relative skill of those in the art is very high.

The predictability or lack thereof in the art:

The skilled artisan would view that the treatment to prevent multiple sclerosis, absolutely, or permanently is highly unpredictable.

The amount of direction or guidance presented and the presence or absence of working examples:

In the instant case, no working examples are presented in the specification as filed showing how to prevent multiple sclerosis totally, absolutely, or permanently. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Genentech, Inc. v. Novo Nordisk, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas

that may or may not be workable".

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether preventing multiple sclerosis totally, absolutely, or permanently.

Claim Rejections. 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 7, 9, 12-15, and 17-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Formula I compounds and their salts, does not reasonably provide enablement for their hydrates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The following reasons apply to this rejection.

The claims, in embracing hydrates, are not enabled. The specification prophesizes hydrates, but the numerous examples presented all failed to produce a hydrate. The evidence of the specification is clear: These compounds

do not possess the property of forming hydrates; there is no evidence that such hydrates even exist.

Applicants' attention is drawn to Revised Interim Utility and Written Description Guidelines, 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." MPEP 2163, *et. seq*. This Application's disclosure is insufficient to enable the instantly claimed hydrates based solely on the disclosure of the compounds and salts, absent the disclosure of a valid method of preparing the hydrates. The state of the art indicates the requirement for undue experimentation.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

(1) Breadth of claims.

(a) Scope of the hydrates. The claims cover potentially millions of hydrates of the claimed compounds of formula I.

(b) Scope of the methods of preparing the hydrates. The scope of methods is stated above, as well as the fact that the specification contains not one disclosure of the preparation of a hydrate of the claimed compounds.

(2) The nature of the invention and predictability in the art:

Preparation of hydrates of the claimed compounds. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and preparation of hydrates are generally considered to be unpredictable. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). In the instant case, the preparation of hydrates is not sufficiently addressed by the instant disclosure.

(3) Direction or Guidance:

That provided is very limited. Not a single hydrate is prepared in the specification. There is no specific disclosure of the specific conditions that will prepare and isolate the claimed hydrates.

(4) State of the Prior Art:

Formation of hydrates is highly compound-specific in organic chemistry. Brittain, Chapter V of Polymorphism in Pharmaceutical Solids,

1999, pages 126-127, catalogs various difficulties of forming, isolating and identifying hydrates:

> Substances may hydrate/dehydrate in response to changes in environmental conditions, processing or over time if in a metastable thermodynamic state.
>
> It may not be practical or possible to maintain the same hydrate isolated at the discovery bench scale synthesis during scale-up activities for a hydrated compound. The choice of counterions to produce a more soluble salt form may also be dictated by the extent and type of hydration observed for a given salt and/or by the moisture level that may be safely accommodated by the dosage form.
>
> The physicochemical stability of the compound may raise issues during preformulation. Some hydrated compounds may convert to an amorphous form upon dehydration and some may become chemically labile. This Is true of cephradine dehydrate that dehydrates to become amorphous and undergoes subsequent oxidation. Other compounds may convert from a lower to a higher state of hydration yielding forms with lower solubility. In any case, the resulting "new" forms would represent unique entities that, depending on the dosage form, might have to be maintained throughout the manufacturing process and in the clinic and would impact on the regulatory status of the compound. Most often this demands that the form (usually crystalline) be identified and characterized with respect to hand-ling conditions during the early pre-IND state of the development process.
>
> As dosage form development proceeds, changes in hydration state can result in variable potencies depending on handling conditions during weighing steps, the kinetics of the hydration/dehydration process, and the environmental conditions during processing. Differences in powder flow can result from changes in crystal form and/or morphology that may accompany the hydration/dehydration process. This can affect content uniformity in solid processing either in the mixing process or during transfer to other processing equipment such as tablet presses. …
>
> During and after manufacturing, moisture from the environment or that sealed in the package may redistribute throughout the dosage form and change the hydration state(s). These changes can, in turn, visit the negative consequences discussed above for the bulk drug on the dosage form. These can be manifest as changes in tablet/capsule dissolution rates (and perhaps bioavailability), changes in lyophile reconstitution times, tablet capping, chemical instability, discoloration and more.

The present specification confirms Brittain. The specification fails to report making, isolating and/or identifying even one hydrate. Applicants must show making and identifying hydrates or cancel them from the claims.

(5) Working Examples:

The specification prophesizes preparing hydrates of all of the claimed compounds, but no working examples or correlative prior art teachings actually show how to make and identify even a single hydrate.

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

> "The first paragraph of 35 U.S.C. 112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

Plant Genetic Syst. v. DeKalb Genet., 65 USPQ2d 1452, 1456 (Fed. Cir. 2003). "[T]he scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(6) Skill of those in the art:

See the discussion of Brittain above. The state of the art supports that to successfully prepare, isolate and identify a hydrate requires specific individualized methods.

(7) The quantity of experimentation needed:

Based on the disclosure content, to make the invention would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure gives the skilled artisan inadequate guidance regarding the method of making, isolating and identifying hydrates, for the reasons stated above.

Discussion of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the breath of the

claims, the unpredictability of methods of making, isolating and identifying hydrates, one of ordinary skill in this art would have to undergo an undue amount of experimentation to make the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

This is a circumstance where the "specification is evidence of its own inadequacy" (*In re Rainer*, 153 USPQ 802, 807). Hydrates cannot be simply willed into existence. *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 states:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist ... the examples of the '881 patent do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The same circumstance appears true here: no evidence shows that hydrates of these compounds actually exist; if they did, they would have formed. Applicants must show making hydrates or limit the claims accordingly.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 7, 9, 12-15 and 17-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maier (PG Pub No. 2004/0122228 A1) of record in view of Hauel (US Patent No. 7,109,192 B2) (aka 2005/0020574 A1) of record in further view of Reinhold (International Conference on Dipeptidyl Aminopeptidases, 2002) of record.

Maier teaches compounds of formula I which overlaps with Applicant's compounds of formula I [0002]-[0267]. The compounds are taught to inhibit dipeptidylpeptidase-IV enzyme (DPP-IV) activity and are suitable for the

treatment of a number of conditions, including autoimmune diseases such as multiple sclerosis [0327].

Maier does not specifically teach the elected specie of 2-(3-aminopiperidin-l-yl)-3-(2-butynyl)-5-methyl-3,5-dihydroimidazo[4,5-d]pyridazin-4-one.

Hauel teaches compounds of formula I which embrace many of Applicant's of formula I, namely the elected specie of 2-(3-aminopiperidin-l-yl)-3-(2-butynyl)-5-methyl-3,5-dihydroimidazo[4,5-d]pyridazin-4-one (column 66, example 114).

Hauel teaches the compounds as demonstrating an inhibitory effect on the activity of the dipeptidylpeptidase-IV enzyme (DPP-IV) and their ability to treat a number of conditions (column 21, lines 26-65).

Reinhold teaches the employment of DPP-IV inhibitors in the treatment of multiple sclerosis (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the compounds of formula I for the treatment of multiple sclerosis as taught by Maier and also employed the specific compound, 2-(3-aminopiperidin-l-yl)-3-(2- butynyl)-5-methyl-3,5-dihydroimidazo[4,5-d]pyridazin-4-one. The motivation, provided by Hauel, teaches that 2-(3-aminopiperidin-l-yl)-3-(2- butynyl)-5-methyl-3,5-dihydroimidazo[4,5-d]pyridazin-4-one, encompassed by an overlapping series of compounds, also designated formula I, are DPP-IV inhibitors. One would expect, with a reasonable degree of success, that the substitution of one DPP-IV inhibitor over another would

demonstrate similar results in the treatment of a condition, in this case, multiple sclerosis, in the absence of unexpected results. While Maier teaches the relevant compounds for a number of diseases, one of which is multiple sclerosis, the number of conditions listed is lengthy. Thus to specifically select the treatment of multiple sclerosis may be considered as "picking and choosing". In as such, Reinhold is employed to demonstrate that in fact DPP-IV inhibitors are effective in treating multiple sclerosis. Thus, one of ordinary skill in the art would be further motivated to employ 2-(3-aminopiperidin-l-yl)-3-(2- butynyl)-5-methyl-3,5-dihydroimidazo[4,5-d]pyridazin-4-one as a method of treating multiple sclerosis based on reasons of record.

In view of the foregoing arguments, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 1, 3, 7, 9, 12-15 and 17-25 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service

Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sahar Javanmard whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627